

REMARKS

Claims 1-4, 6-17 and 19 were pending in the application. In the Office Action mailed June 14, 2006 (the "Office Action"), claims 6-17 and 19 are withdrawn from consideration as being directed to non-elected groups, and claims 1-4 are rejected. In the instant Amendment, claims 2, 7 and 19 have been canceled, without prejudice, claims 1, 3-4, 6, 8-9, and 14-16 have been amended, and new claims 20-22 have been added to clarify the claimed invention. Upon entry of the instant Amendment, claims 1, 3-4, 6, 8-17 and 20-22 will be pending in the application.

Claim 1 has been amended to clarify that the AHP comprises (a) a monoclonal antibody that specifically binds a complement receptor (CR1) site on a primate erythrocyte, and (b) an antigen specific for a target pathogenic antibody or autoantibody. Support for the amendment can be found in the specification at page 7, lines 14-15. Claims 6 and 14-16 have been amended similarly.

Claims 3 and 4 have been amended to include the following additional antigens: desmogleins, desmoplakins, antigens found on heart muscle, and antigens associated with immune complex kidney disease. Support for the amendment can be found in the specification at, *e.g.*, at page 8, line 18 to page 9, line 5. Claims 8 and 9 have been amended similarly.

Claim 6 has been amended to delete steps 2) and 3). Support for the amendment is found in the specification at page 3, lines 19-26 and page 13, lines 1-6.

Claim 14 has been amended to delete steps 2) and 3). Support for the amendment is found in the specification at page 3, lines 19-26, page 12, lines 10-17, and page 13, lines 1-6.

Claim 15 has been amended to delete steps 3) and 4). Support for the amendment is found in the specification at page 13, lines 20-26.

Claims 6 and 14-16 have also been amended to clarify that the term "AHP" stands for "antigen-based heteropolymer."

New claims 20-22 have been added. These claims recite the deleted steps in the original claims 6, 14 and 15, respectively.

No new matter has been introduced by these amendments.

1. The Rejections of Claim 2 Under 35 U.S.C. § 112, Should Be Withdrawn

Claim 2 was rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement because the mAbs 1B4, HB8592, and 7G9 are allegedly not deposited at an acceptable depository. Claim 2 was also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the claims allegedly recite the laboratory names of mAbs 1B4, HB8592, and 7G9. Applicants have canceled claim 2. The rejections are therefore obviated.

2. The Rejection of Claims 1-4 Under 35 U.S.C. § 103(a), Should Be Withdrawn

Claims 1-4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Taylor et al., J. Immunol. 1992. 148(8): 2462-2468 ("Taylor") in view of Kimberly et al., J. Clin. Invest. 1989. 84(3): 962-970 ("Kimberly") and Emlen et al., J. Immunol. Meth. 1990. 132(1): 91-101 ("Emlen"). In the Office Action mailed June 14, 2006 (the "Office Action"), the Examiner contends that it would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of Taylor, Kimberly, and Emlen in order to facilitate erythrocyte-mediated removal of anti-dsDNA antibodies from the peripheral blood of primates with an autoimmune disease (see, the Office Action, page 5, last paragraph). Applicants respectfully disagree with the Examiner for reasons set forth below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). When selective combination of prior art references is required to render obvious a subsequent invention, "there must be some reason for the combination other than the hindsight gleaned from the invention itself. There must be 'something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'"

Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985). The case law has held that if a reference teaches away from combining with another reference, then there is no suggestion to combine. For example, in *Tec Air, Inc., v. Denso Manufacturing Michigan Inc.*, the Federal Circuit held that “[t]here is no suggestion to combine, however, if a reference teaches away from its combination with another source” and that “[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant ... [or] if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant” *Tec Air, Inc., v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). The case law has been especially vigorous on guarding against using “hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.” See, e.g., *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The case law further held that each reference must be evaluated as a whole, i.e., disclosures in the reference that diverge from and teach away from the invention cannot be disregarded. “Not only must the claimed invention as a whole be evaluated, but so also must the references as a whole, so that their teachings are applied in the context of their significance to a technician at the time--a technician without our knowledge of the solution.” *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

The presently claimed invention relates to an antigen-based heteropolymer (AHP) comprising (a) a monoclonal antibody that specifically binds a complement receptor (CR1) site on a primate erythrocyte, and (b) an antigen specific for a target pathogenic antibody or autoantibody, in which the monoclonal antibody is crosslinked to the antigen. The AHP, when administered to a human or non-human primate, facilitates binding of the target pathogenic antibody or autoantibody to erythrocytes and subsequent clearance of the target pathogenic antibody or autoantibody from the circulation of the human or non-human primate. The presently claimed invention also relates to erythrocytes franked with the AHP and to methods for treating or detecting an autoimmune disease using the AHP.

Taylor teaches a bispecific heteropolymer comprising a first mAb that binds a CR1 receptor on a primate erythrocyte and a second mAb that binds the DNP-bovine γ -globulin (DNP-BGG) (see Taylor Abstract). Taylor teaches that injection in squirrel monkeys of DNP-BGG followed by the heteropolymer leads to E binding and clearance from the

circulation of a significant fraction of both the heteropolymers and the DNP-BGG (see Taylor Abstract). Taylor suggests that the the method can be used to treat diseases associated with blood-borne pathogens (see Taylor Abstract). Taylor also showed that partial heteropolymers lacking the second mAb were not cleared (see, e.g., Taylor at page 2467, right column, 4th paragraph). Taylor suggests that the “mechanism of clearance may involve recognition of Fc regions of IgG not directly associated with CR1”, i.e., of the non-anti-CR1 IgG (see, e.g., Taylor at page 2467, right column, 4th paragraph). Taylor does not teach or suggest an antigen-based heteropolymers (AHP) comprising an anti-CR1 antibody crosslinked to an antigen that is recognized by a pathogenic antibody or autoantibody. Nor does Taylor teach or suggest that such an AHP can be used to clear pathogenic antibody or autoantibody.

Kimberly discloses a study of in vivo handling of soluble complement fixing Ab/dsDNA immune complexes in chimpanzees. Kimberly teaches that C-fixing antibody/dsDNA immune complexes bound efficiently to erythrocytes of chimpanzees (see Kimberly Abstract). The chimpanzee erythrocyte-bound IC can be stripped from the erythrocyte rapidly by the mononuclear phagocyte system without sequestration of the erythrocyte (see Kimberly Abstract). Kimberly does not concern heteropolymers or antigen-based heteropolymers. Thus, although Kimberly teaches antibody/dsDNA immune complexes can be cleared by an IC-mediated process, Kimberly does not teach or suggest that an AHP can be used to clear a pathogenic antibody or autoantibody.

Emlen teaches an ELIZA assay for the detection of antibodies that bind double-stranded DNA. Emlen teaches biotinylating dsDNA such that they can be bound to streptavidin coated wells (see Emlen Abstract). The well-bound DNAs remained double stranded, and did not lose their antigenicity to their antibodies (see Emlen Abstract). Emlen does not concern heteropolymers or antigen-based heteropolymers. Nor does Emlen relate to clearance of antibodies/dsDNA complexes in the circulation of a primate.

Applicants respectfully point out, as the Examiner has recognized in the Office Action (see, the Office Action, page 4, last two paragraphs), that Taylor teaches bispecific heteropolymers comprising a first mAb that binds a CR1 receptor and a second mAb that binds a circulating antigen, but not an AHP that comprises an anti-CR1 antibody crosslinked to an antigen. Taylor does not teach or suggest modifying its bispecific heteropolymer by replacing the second mAb in its bispecific heteropolymer with an antigen so as to create an

AHP. Instead, Taylor teaches that the Fc regions of the second antibody are required for clearance. Thus, Taylor not only does not teach or suggest modifying its bispecific heteropolymer by replacing the second mAb with an antigen, but also teaches against making such a modification as it would render the resulting product unsuitable for its intended purpose, i.e., clearance of pathogens.

Neither Kimberly or Emlen supplies what is missing in Taylor. As discussed above, although Kimberly teaches antibody/dsDNA immune complexes can be cleared by an IC-mediated process, Kimberly does not teach or suggest that an AHP can be used to clear a pathogenic antibody or autoantibody. Although Emlen teaches biotinylating dsDNA such that it can be bound to streptavidin coated wells and retain its antigenicity, Emlen does not relate to heteropolymers or antigen-based heteropolymers, much less clearance of antibodies/dsDNA complexes in the circulation of a primate using such heteropolymers or antigen-based heteropolymers. Thus, neither Kimberly or Emlen teaches or suggests modifying Taylor's bispecific heteropolymer to generate the AHP of the present invention. In addition, neither Kimberly or Emlen suggest to a person skilled in the art that the Fc regions of the second antibody are not required for clearance, and, thus, that an AHP, which lacks such Fc regions, would be able to achieve the purpose of clearance of pathogens. Thus, neither Kimberly or Emlen provide teachings to a person skilled in the art that would overcome the discouragement provided by Taylor. As such, neither Talyor, Kimberly, or Emlen, alone or in combination, provide to a person skilled in the art the suggestion and the reasonable expectation of success to modify Taylor's bispecific heteropolymer to create the AHP of the present invention.

In the Office Action, the Examiner contends that "the artisan would have reasonably expected that replacing the biotinylated second antibody of the complex taught by Taylor with the biotinylated dsDNA of Emlen would create a complex comprising an anti-CR1 antibody and an antigen specific for ... a target pathogenic antibody or autoantibody that is useful for facilitating erythrocyte-mediated removal of the target pathogenic antibody or autoantibody" (see, the Office Action, page 5, last paragraph). Applicants respectfully point out that, as discussed above, Taylor teaches that the Fc regions of the second antibody are required for clearance. Since replacing the second antibody in Taylor's bispecific heteropolymer with an antigen would result in the loss of such Fc regions, a person skilled in the art would expect, based on Taylor's teachings, that an AHP, due to its lack of such Fc

regions, would not provide for clearance of the target antibody or autoantibody. “A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant ... [or] if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant” *Tec Air, Inc., v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). Thus, Taylor teaches away from present invention.

Applicants further respectfully submit that the combination of the references put forth by the Examiner is a result of hindsight reconstruction. The Examiner fails to evaluate each reference as a whole, but instead, disregards disclosures in the references that diverge from the invention. As discussed above, Taylor teaches that the Fc regions of the second antibody are required for clearance. A person skilled in the art would expect that an AHP, due to its lack of such Fc regions, would not allow clearance of the target antibody or autoantibody. Thus, a person skilled in the art would not be motivated to combine Taylor, Kimberly, and Emlen in the manner suggested by the Examiner. The combination of the references suggested by the Examiner is clearly a result of “hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention” (See, e.g., *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)), in which the disclosures in the reference that diverge from and teach away from the invention were disregarded. Such hindsight reconstruction is improper.

In view of the foregoing, Applicants respectfully submit that claims 1-4 are not rendered obvious under 35 U.S.C. § 103(a) by Taylor in view of Kimberly and Emlen, and that the rejection of these claims under 35 U.S.C. § 103(a) based on Taylor in view of Kimberly and Emlen should be withdrawn.

3. Claims Withdrawn From Consideration As Belonging To Non-Elected Groups Should Be Considered

Claims 6-17 and 19 were withdrawn from consideration by the Examiner as belonging to a non-elected group. These claims incorporate all the limitations recited in the product claims. Since Applicants believe that the product claims are allowable, claims 6-17 and 19 should be considered by the Examiner. Applicants respectfully request that these claims be considered by the Examiner.



CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history of the present application. Applicants submit that the presently pending claims meet all requirements for patentability and respectfully request allowance and action for issuance.

Applicants request that the Examiner call the undersigned at (212) 326-3939 if any questions or issues remain.

Respectfully submitted,

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